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EXAMINER

BAKER, A

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/963,288	Applicant(s) Norstedt et al.
	Examiner Anne-Marie Baker, Ph.D.	Group Art Unit 1632

Responsive to communication(s) filed on May 26, 1999 and August 30, 1999.

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

Claim(s) 1, 2, 5-11, 15-17, and 19-38 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

Claim(s) 1, 2, 5-11, 15-17, and 19-38 is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION

The amendments filed May 26, 1999 (Paper No. 9) and August 30, 1999 (Paper No. 10) have been entered. Claims 1-2, 5-7, 9-11, 15-17, 25, 27, 30, and 34 have been amended. Claims 3, 4, 12-14, and 18 have been cancelled. Claims 19-38 have been newly added. Thus, Claims 1-2, 5-11, 15-17, and 19-38 are pending in the instant application.

The following rejections constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn.

Priority

Applicants' comments and documentation concerning the priority to which the instant application is entitled have been fully considered. The application is granted priority to October 21, 1994, the filing date of Swedish Application No. 9403613-4 to which priority is claimed in the international application PCT/SE95/01235, filed October 19, 1995.

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Sweden on October 21, 1994. It is noted, however, that applicant has not filed a certified copy of the Swedish application as required by 35 U.S.C. 119(b).

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Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5-11, 15-17, and 19-38 stand and are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of enhancing transcription *in vitro* using an SPI-growth hormone responsive element (SPI-GHRE) and lactogenic stimuli, does not reasonably provide enablement for the claimed enhancer element, any method of enhancing transcription *in vivo*, or a method of enhancing transcription *in vitro* or *in vivo* using any enhancer element comprising the nucleotide sequence TTC TGA GAA and exposing the DNA construct to lactogenic stimuli. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Claims 1, 2, 5-11, and 15-17 stand rejected under 35 U.S.C. 112, first paragraph for reasons of record advanced on pages 3-5 in the previous Office Action mailed 2/25/99 (Paper No. 7). Newly added Claims 19-38 stand rejected for the same reasons and are further rejected on the grounds that the instant specification does not teach how to use the claimed enhancer element, expression vectors, or DNA constructs for anything other than *in vivo* applications. For reasons of record advanced in the previous Office Action (Paper No. 7), the specification fails to provide an enabling disclosure for the method of enhancing transcription *in vivo* using any enhancer element comprising the nucleotide sequence TTC TGA GAA because one cannot predict whether results obtained *in vitro* would be obtained *in vivo*.

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The specification fails to provide an enabling disclosure for the method of enhancing transcription *in vitro* using any enhancer element comprising the nucleotide sequence TTC TGA GAA because one cannot predict whether any and all enhancers comprising this nucleotide sequence would be responsive to lactogenic stimuli. Example 1 of the instant specification indicates that Applicants have demonstrated that the core SPI-GAS sequence, TTC TGA GAA, functions as a growth hormone (GH) regulated DNA element *in vitro* when put into a reporter vector. Example 2 indicates that both prolactin and growth hormone activate expression from SPI-TK-reporter gene constructs *in vitro* and that the results obtained with the SPI-GAS element (or SPI-GLE) were similar to the results obtained with the 50 bp SPI-GHRE enhancer. This experiment does not demonstrate that other enhancers that contain the SPI-GAS element would be responsive to lactogenic stimuli.

Applicants argue that there is a correlation between *in vitro* and *in vivo* responsiveness of SPI-GHRE to growth hormone because Yoon et al. (1987) teach that expression of Spi-1 and Spi-2 are induced upon administration of growth hormone to hypophysectomized rats. This experiment only demonstrates that the native construct comprising all of the naturally-occurring upstream genetic elements is susceptible to growth hormone induction *in vivo*. As discussed in the previous Office Action (Paper No. 7) Lavenu et al. (1994) and Petitclerc et al. (1995) demonstrated the importance of context of *in vivo* genetic elements through their experiments. Applicants do not address these findings nor their relevance to extrapolating *in vivo* function of genetic elements from *in vitro* observations. The teachings of Petitclerc et al. and Lavenu et al. are directly relevant to the instantly claimed invention.

Claims 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

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relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants are referred to the interim guidelines on written description published June 15, 1998 in the Federal Register at Volume 63, Number 114, pp. 32639-32645 (also available at www.uspto.gov).

Claims 9 and 10 are directed to an expression vector comprising an enhancer element including the nucleotide sequence TTC TGA GAA, wherein the promoter is a thiamine kinase promoter. Neither the instant specification nor the prior art provide any evidence for the existence of a “thiamine kinase promoter.” Thus, the specification does not contain a written description of the claimed expression vector. The specification does not disclose the claimed subject matter at all. The response contends that the “thiamine kinase promoter” is described at page 3, line 8 of the specification. However, the specification refers to the thymidine kinase promoter not a thiamine kinase promoter. Thus, the written description is not sufficient to inform the skilled artisan that Applicants were in possession of the claimed invention at the time of filing.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9, 10, and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9 and 10 are indefinite in their recitation of a “thiamine kinase promoter” because neither the instant specification nor the prior art provide any evidence for the existence of a “thiamine kinase promoter.”

Claim 23 is indefinite in its recitation of “transection” because its use in this context does not make sense. It appears to be a typographical error which should read as “transfection.”

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Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

While the specification does not explicitly define "lactogenic stimuli," it is known in the art that human growth hormone can bind to both lactogenic and somatogenic receptors with high affinity (Le Stunff et al., 1996). Therefore, growth hormone is considered to be included as "lactogenic stimuli."

Claims 1 and 2 stand rejected under 35 U.S.C. 102(b) as being anticipated by Yoon et al., 1990 for reasons of record advanced in the previous Office Action (Paper No.7) on pages 10-12

Applicants do not offer any arguments regarding the rejection of Claims 1 and 2 under 35 U.S.C. 102(b).

Applicants argue that the newly added claims are limited to methods and compositions that use or include the nucleotide sequence TTCTGAGAA, with the proviso that the nucleotide sequence is not the DNA sequence of SPI-GHRE. Applicants argue that Yoon et al. (1990) provides no teaching or suggestion of a segment smaller than the 50 bp segment set forth as SPI-GHRE which is responsive to growth hormone and that there is nothing in Yoon et al. to teach or suggest the use of the 9 bp sequence recited in the claims. Only Claims 1 and 2 are rejected as anticipated by Yoon et al. Claims 1 and 2 are not limited to the use of an enhancer element smaller than the 50 bp segment taught by Yoon et al. as SPI-GHRE. Claim 2 is specifically

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directed to the use of SPI-GHRE in a method of enhancing transcription. This teaching is clearly disclosed by Yoon et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5-11, 15-17, and 23-33 rejected under 35 U.S.C. 103(a) as being unpatentable over Lindquester et al. (1989).

The claims are directed to an enhancer element comprising the nucleotide sequence TTCTGAGAA, an expression vector comprising at least one enhancer element including the nucleotide sequence TTCTGAGAA, an isolated eukaryotic host cell containing the expression vector, and a DNA construct comprising a promoter, a structural gene and at least one enhancer element comprising the sequence TTCTGAGAA.

Lindquester et al. (1989) disclose the nucleotide sequence of an avian tropomyosin gene. The gene includes the sequence TTCTGAGAA located in one of the introns (position 18602 of Figure 1 on page 2105). A genomic clone containing the tropomyosin gene was isolated from a quail DNA genomic library.

Since enhancer elements are known to be located in introns, the presence of the sequence TTCTGAGAA in an intron would permit it to function as an enhancer element. The hormone responsiveness of the element is an inherent property of the element. Thus, even if the hormone responsiveness of the genetic element was not recognized, the presence of the DNA sequence would confer hormone responsiveness to the

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disclosed gene. Furthermore, one would have been motivated to construct an expression vector comprising the tropomyosin gene and a host cell comprising said expression vector in order to produce the protein in culture. One would have anticipated a reasonable expectation of success for making the expression vector and host cell comprising the expression vector because only standard molecular biology techniques are required to make such compositions. Therefore, it would have been obvious to one of skill in the art at the time of the invention to have made an expression vector and a host cell comprising the expression vector, wherein the expression vector comprises an enhancer element including the nucleotide sequence TTCTGAGAA.

One would have been motivated to use the nucleotide sequence disclosed by Lindquester et al. to construct an expression vector and a host cell comprising the expression vector in order to produce tropomyosin in culture for further study of the protein and the regulatory sequences driving expression of the protein.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Friday from 8:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Stanton, can be reached on (703) 308-2801. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Anne-Marie Baker, Ph.D.



BRUCE R. CAMPELL
PRIMARY EXAMINER
GROUP 1800